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Prenatal Diagnosis of Osteochondrodysplasias in High Risk Pregnancy

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We collected data on 39 prenatally diagnosed osteochondrodysplasias. We detected 30 (76.9%) cases in the first and second trimesters, including 18 (46.2%) with two twins before the 24th week of gestation. Of 39 cases 11 (28.2%) had osteogenesis imperfecta (OI) type II. Verification of the prenatal diagnosis was attempted in 26 cases on the basis of the data obtained from ultrasonographs, radiographs, external examination, and autopsy protocols. The prenatal diagnosis was confirmed in 19 (73%) fetuses. In 13 cases verification was not possible because one or several investigations could not be performed. Counselling followed all identified cases with osteochondrodysplasia. We present the pedigree of two families indicating the possibility of early prenatal diagnosis of achondrogenesis type I and metatropic dysplasia. We propose indications for ultrasonographic anatomical screening with subsequent phenotype analysis in high risk pregnancy to provide for the prenatal detection of malformations and hereditary diseases.

KEY WORDS: osteochondrodysplasias, fetus, prenatal diagnosis, ultrasonography

INTRODUCTION

In the Ukraine congenital and hereditary diseases are one of the main reasons of mortality and handicap in newborn infants. The most frequent defects are congenital heart and skeletal anomalies. Among 42,012 families referred for consultation to the Kharkov Interregional Medico-Genetic Centre over 10 years (1986–1995) skeletal anomalies were diagnosed in 1672 (3.98%) cases. The birth prevalence was estimated to be 3.16 per 10,000 births. Rasmussen et al. [1996] identified 49 cases of osteochondrodysplasia among 126,316 deliveries over a 15-year period. They estimated the prevalence (with exclusion of high risk patients) at 2.14 per 10,000 deliveries and presented a range of rates for 14 specific types of osteochondrodysplasias.

Unfortunately, the prevalence of most types of osteochondrodysplasias in the population is unknown [Kozlova et al., 1987]. One of the reasons is the complicated classification which varies not only from country to country but from the specialist to the specialist (sonographer, radiographer, orthopaedist, geneticist, etc.). For prenatal diagnosis the International Nomenclature of Constitutional Diseases of Bone [Spranger, 1992] is more suitable. Much attention must be paid to the distinction between lethal and non-lethal types, because of the necessity to decide in time the issue of pregnancy management. The absence of effective methods of treatment and fetal prophylaxis increased the need for early detection of these disorders. Although several hundred skeletal dysplasias have been described, only a few of them can be recognized with the use of sonography in the antepartum period [Brons et al., 1988; Romero et al., 1988; Grechanina et al., 1989; Lachman, 1994].

Despite thoroughly performed ultrasonographic scanning, verification of diagnosis in most cases is possible only by comparison of radiographs obtained postnatally or after termination with the patterns presented in the atlases of radiograms [Spranger et al., 1974; Cremin et al., 1978; Ornoy et al., 1988] and the OSSUM software system. For diagnostic purposes histological examination of the chondro-osseous tissue, biochemical and chromosome analysis should also be considered. Prenatal diagnosis of osteogenesis imperfecta (OI) by DNA linkage analysis in chorionic villi or in amniocytes has been reported [Smith, 1996].

Our objective was to perform sonographic scanning in high-risk pregnant women by using a special approach to obtain an image of the fetus compatible with radiograms and in order to correctly diagnose the type of osteochondrodysplasia prenatally.

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Dedicated to Jürgen W. Spranger on the occasion of his 65th birthday with admiration and best wishes.

MATERIALS AND METHODS

Ultrasound studies were carried out in 12,200 high risk pregnant women between 9 and 40 weeks of gestation. Real time scanners ALOKA-630 SSD and TOSHIBA 50 SAL with 3.5 and 5.0 MHz transducers were used in conjunction with fetal nomogrammes developed for the Ukrainian population [Gordienko, 1992]. The investigations followed a systemic approach, the whole skeleton being studied by anatomical screening with subsequent phenotype analysis. The following parameters were measured and studied individually: biparietal diameter, head, thoracic and abdominal circumference, femur, humerus, tibia, fibula, radius, ulna, vertebral bodies, scapula, clavicle, ribs, and pelvis. Much attention was paid to the visualisation of the face, especially the forehead, nose, nasolabial triangle, orbits, interorbital distance, and chin. To exclude syndactyly, polydactyly, or other anomalies feet and hands were examined thoroughly. An estimate of the degree of mineralisation and of bone density was obtained as well. Most cases were examined repeatedly. Taking into account the difficulties in prenatal diagnosis of osteochondrodysplasia all examinations in high risk pregnant women were performed only by experienced staff. Autopsy was carried out on all dead fetuses, in some of them supplementing with histologic analysis of bone and cartilage. Before autopsy, whole-body radiographs and photographs were obtained using standardized techniques. Counselling was provided in all cases of osteochondrodysplasia.

RESULTS

We examined 12,200 high risk pregnant women in the Fetal Medicine Department of the Kiev Institute of Paediatrics, Obstetrics and Gynaecology. We combined indications for ultrasonographic anatomical screening with subsequent phenotype analysis in high risk pregnancies to provide the prenatal detection of congenital malformations and hereditary diseases. Attention was paid not only to the risk factors from the history, but also to those that appeared in the current pregnancy:

1. Family history for abnormalities (including chondrodysplasias).
2. Extragenital diseases (diabetes mellitus, thyroid gland diseases).
3. Perinatal death of two or more previous children.
4. The threat of miscarriage, especially bleeding in the early pregnancy.
5. Uterus too small or too big for the gestational age.
6. Polyhydramnios.
7. Olygohydramnios.
8. Movement abnormalities.
9. Multiple pregnancy.
10. Suspected fetal anomalies during the ultrasonographic monitoring.

Of 12,200 women examined we diagnosed prenatally 520 congenital malformations and hereditary diseases in the fetus including 39 (7.5%) cases of osteochondrodysplasias (Table I). We detected 30 (76,9%) of all cases with osteochondrodysplasias in the first two trimesters, including 18 (46.2%) before the 24th week of gestation(Figs.1–9).

The prenatal diagnosis was verified in 26 (66.6%) cases by means of comparison of data obtained from ultrasonographs, radiographs, external examination and, autopsy protocols. In 19 (73%) fetuses there was concurrence of prenatal, postnatal, or post-abortion diagnoses. Among the causes of failure to verify the other 13 cases of osteochondrodysplasias (predominantly at a late stage of gestation) were the following: the absence of radiological investigation postnatally, non-response of the pregnant women for invitation to continue examination, admittance of the pregnant women for labour, or termination of pregnancy to other hospitals. In these cases only the ultrasonographic images were available for purposes of diagnosis. Taking into account the 73% concurrence rate of ultrasonographic images in our investigations with verified cases of osteochondrodysplasias, we hope that in most of the nonverified cases the prenatal diagnosis was correct.

Of the 39 cases of osteochondrodysplasias 11 (28.2%) fetuses had OI type II. The reason for this high proportion could be admittance of pregnant ascertainment bias or possible mutation impact due to the Chernobyl accident.

The possibility of the early diagnosis of metatropic dysplasia (Figs. 10, 11) and achondrogenesis type I (Fig.12) is documented in the pedigrees of Case G. (Fig.13) and Case N. (Fig.14).

Case G

This pregnant woman was sent for ultrasound examination because in 1985 she had delivered a child with chondrodysplasia of unknown type who died soon after the birth (II-1). A healthy girl was born in 1987 (II-2). During the ultrasonic examination in 1988 at 25 weeks of gestation the diagnosis of diastrophic dysplasia was suspected. After a termination of the pregnancy and a review of the radiographs the diagnosis was changed to metatropic dysplasia (Fig. 10). The same disorder occurred in a female fetus (II-4) in 1989. Termination of pregnancy was performed at 17 weeks of gestation (Fig. 11). The diagnosis was confirmed by radiographs and autopsy. In 1992 with the help of sonographic examination metatropic dysplasia was diagnosed at 11 weeks of gestation in fetus II-5. The pregnancy was terminated. The pathologists confirmed the diagnosis, the fetus is stored at the Department of Pathomorphology.

Case N

Family N. (consanguineous marriage) was referred in 1988 for counselling because each of their three children had died (1984, 1985, and 1987) several days after delivery (IV-4, 5, 6). The clinical diagnoses were the same: sepsis, pneumonia, and infectious enterocolitis. The appearance of children was normal and parents refused the autopsy. The final diagnoses were unknown, but hereditary metabolic disorders with autosomal recessive inheritance were suspected. During the subsequent pregnancy of Mrs N., the ultrasound examination was performed at 20 weeks of gestation and Roberts syndrome or achondrogenesis was suspected. The pregnancy was terminated. The radiographs and

TABLE I. Verification of the Prenatal Diagnosis of the Osteochondrodysplasias

Osteochondrodysplasia	Gestational age (weeks)	Number of cases	Verified diagnosis (+)
Osteogenesis imperfecta (OI) Type IIA	20	1	+
"-"	20	1	+
"-"	22	1	+
"-"	27	1	–
"-"	28	1	–
Osteogenesis imperfecta (OI) Thpe IIB			
Twins	19	2	++
	24	1	+
	32	1	–
Osteogenesis imperfecta (OI) Type IIC	23	1	+
"-"	25	1	+
Achondroplasia	26	1	+
"-"	32	1	–
"-"	34	1	+
"-"	34	1	–
"-"	35	1	–
Hypochondrogenesis			
Twins	23	2	++
	24	1	+
	26	1	–
	29	1	–
Short Rib-Polydactyly syndrome			
Type Noonan-Saldino	19	1	+
"-"	24	1	+
Type Majewski	19	1	–
"-"	24	1	–
Thanatophoric dysplasia	22	1	–
"-"	26	1	+
"-"	30	1	–
Metatropic dysplasia	11	1	+
"-"	17	1	+
"-"	25	1	+
Achondrogenesis			
Type I	10	1	+
"-"	20	1	+
Type II	23	1	+
Campomelic syndrome	32	1	+
"-"	32	1	–
Diastrophic dysplasia	22	1	+
Chondroectodermal dysplasia	24	1	+
Asphyxiating thoracic dysplasia	22	1	+
TOTAL		39	26(+)

autopsy confirmed the diagnosis of achondrogenesis type I (IV-7). Next year the ultrasonographic examination at 9–10 weeks of gestation was attempted and the same pathology of fetus was suspected. The termination was performed at 17 weeks of gestation and achondrogenesis type I was confirmed by radiographs (Fig. 12) and autopsy (IV-8).

DISCUSSION

The prenatal diagnosis of osteochondrodysplasia and management of the pregnancy in such cases is a difficult problem which involves not only medical but social and ethic aspects as well. Until recently it was difficult to diagnose many fetal anomalies prenatally. But after the introduction of real-time ultrasonography it became easier to establish a correct diagnosis of fetal malformations including osteochondrodysplasias [Hill et al., 1983]. With progress in technology the number of the diagnostic mistakes, which depended on the quality of resolution of the ultrasound unit, decreased significantly [Boog, 1988]. Nowadays, with adequate sonographic equipment for diagnostic purposes, the success of the fetal examination is more dependent on the experience of the specialist. But findings on ultrasonography often are not pathognomic of a particular osteochondrodysplasia [Donnenfeld and Mennuti, 1987]. In a study reported by Sharony et al. [1993], the specific ultrasound diagnosis was incorrect in over half of the 226 fetuses referred to the International Skeletal Dysplasia Registry. The higher concurrence of diagnoses in our investigation can be explained by the significant proportion of families with a history for known osteochondrodysplasias and fetuses with osteogenesis imperfecta type II.

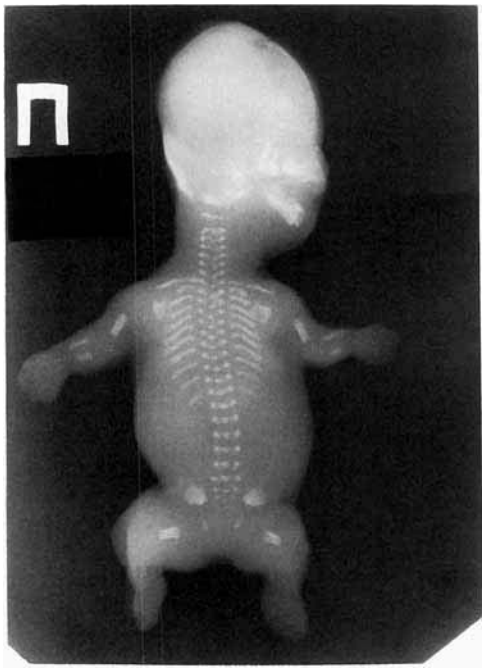

Fig. 1. Fetus with short rib-polydactyly syndrome (Noonan-Saldino type) at 19 weeks of gestation (Case K., 1987).

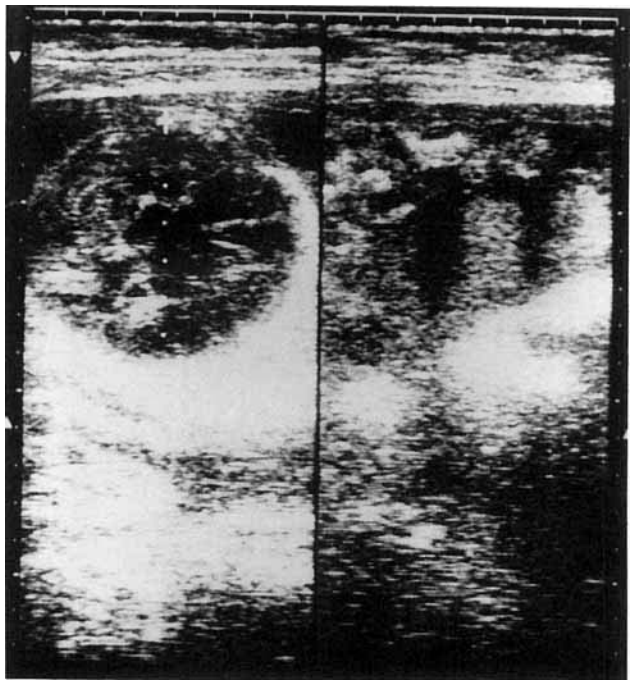

Fig. 2. Ultrasonogram of fetus affected with osteogenesis imperfecta type II A at 20 weeks of gestation (Case P., 1987). There is a disproportionately large head (BPD=86 mm) and short femur (FL=18 mm). Note absence of skull ossification.

There are several approaches in providing ultrasound investigation for pregnant women. One consists in monitoring all pregnant women (level I), and after suspicion of fetal anomaly sending them for more thorough examination (level II) for diagnosis clarification. Unfortunately, some women reach level II too late for proper management of pregnancy. Thus for the purpose of early detection of an abnormal fetus it is extremely important to make an accurate inventory of the risk factors for the pregnant woman as soon as she is referred for the first time to the obstetrician. This inventory must be revised during the course of the pregnancy. Of course many defective children are born by healthy woman with normal pregnancy. But when we analysed retrospectively every one of the 39 prenatally diagnosed fetal chondrodysplasias, we always *found one or more indications of risk factors*. Women in a high risk group must be sent as early as possible for the special anatomical ultrasound examination with subsequent phenotype analysis. This requires from the sonographer knowledge of normal and abnormal morphology and dimensions of the normal fetal skeleton [Brons et al., 1988; Romero et al., 1988]. There should also be close collaboration between the obstetrician, geneticist, pathologist, orthopaedist, etc. for proper diagnosis of the given type of fetal osteochondrodysplasia. The use of prenatal diagnosis in the osteochondrodysplasias may prevent the delivery of a stillborn infant or of an infant destined for early death [Rasmussen et al., 1996]. The problem remains for a liveborn with non-lethal osteochondrodysplasias with crippling consequences.

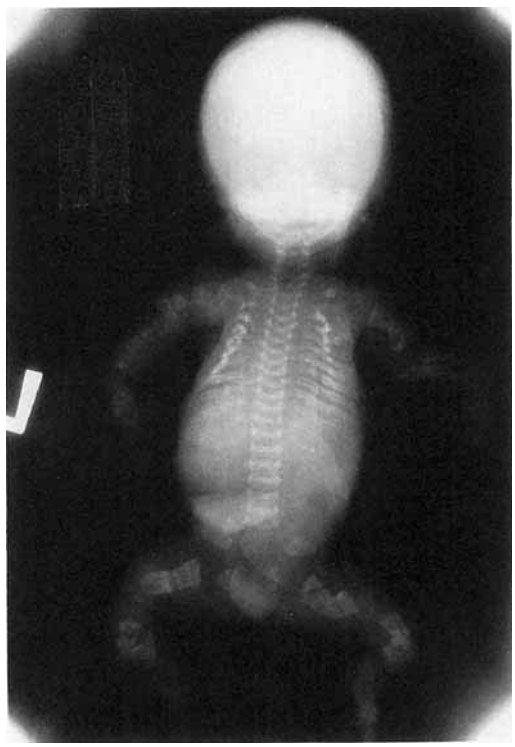

Fig. 3. Fetus with osteogenesis imperfecta type II A at 20 weeks of gestation (Case O., 1993). Note osteopenia of the cranial vault, beading of the ribs, and multiple fractures of long bones.

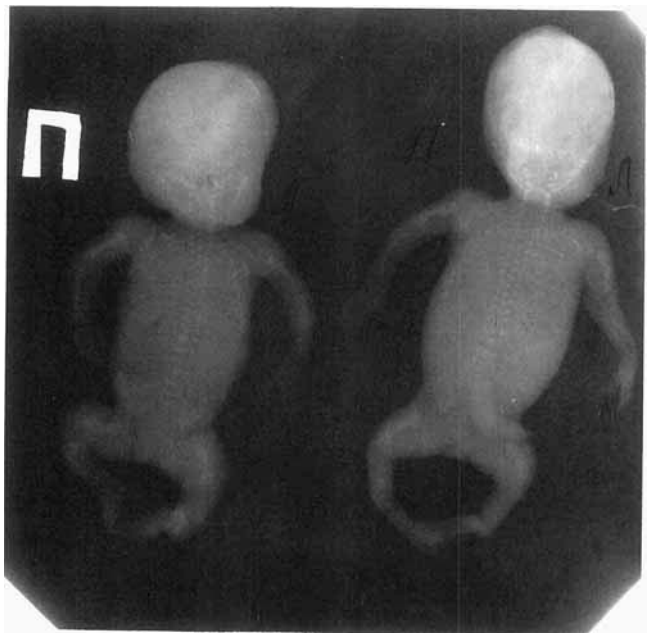

Fig. 4. Twins affected with osteogenesis imperfecta type II B at 18 weeks of gestation (Case S., 1991).

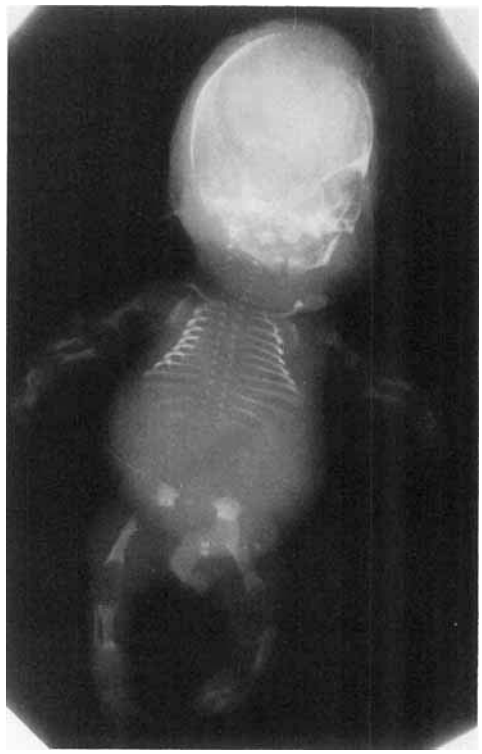

Fig. 6. Fetus with achondrogenesis type II at 23 weeks of gestation (Case M., 1995). The long bones are short and bowed with flare and cupping of metaphyses. The vertebral bodies are minimally ossified.

Nowadays diagnosis may be aided molecular and biochemical approaches. A recent example is the identification of the mutation of genes in some of the types of chondrodysplasias or the detection of deficient enzyme activity as in achondrogenesis type B [Superti-Furga, 1994]. In a dominantly inherited form of osteogenesis

Fig. 5. Case S., 1991. Twins with osteogenesis imperfecta type II B at 18 weeks of gestation.

Fig. 7. Case M., 1995. Fetus with achondrogenesis type II at 23 weeks of gestation. There is nearly total absence of the palate.

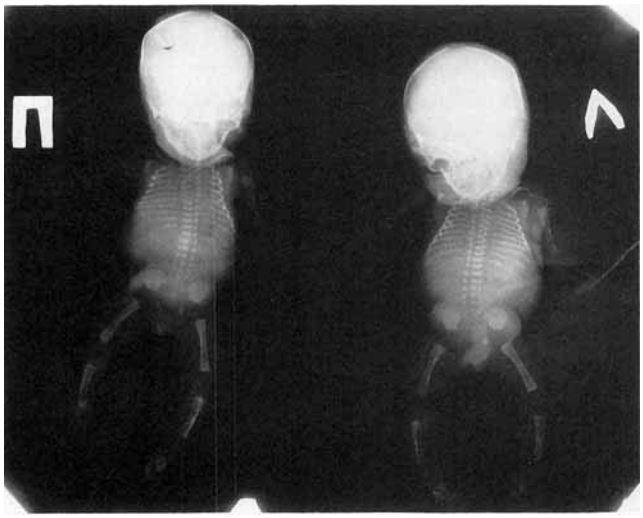

Fig. 8. Twins with hypochondrogenesis at 23-24 weeks of gestation (Case L., 1989). The long bones are straight; the vertebral bodies are less developed in the cervical and sacral regions.

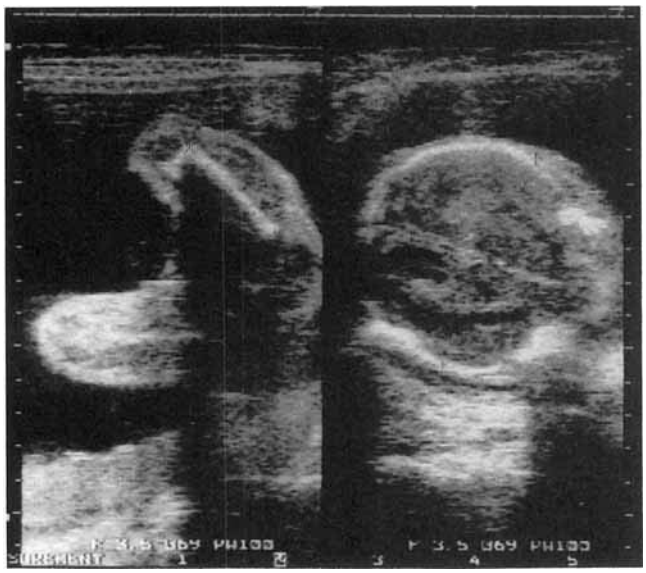

Fig. 9. Ultrasonogram of fetus with hypochondrogenesis at 24 weeks of gestation (Case P., 1995). BPD=68 mm, FL=35 mm.

imperfecta analysis of DNA from affected and unaffected relatives can establish linkage to a particular collagen gene polymorphism. In such a situation analysis of chorionic villus DNA is the most direct approach for prenatal diagnosis [Smith, 1996]. But even with the achievements in molecular genetics, Maroteaux [1995] is correct in that clinical and radiological data still have the final word in diagnosis of bone dysplasias. The crucial role in prenatal diagnosis of these disorders is the method of ultrasonography. The comparison of sonographic pictures with detailed radiographic images and data obtained from a carefully conducted autopsy together and the hystopathological examination of carti-

Fig. 10. Fetus with metatropic dysplasia at 25 weeks of gestation (Case G., 1989). The long bones are short with trumpet-like flare of metaphyses. Note platyspondyly with gross widening of the disk spaces and defective mineralization of the lower lumbal vertebrae. Relatively big hands and feet.

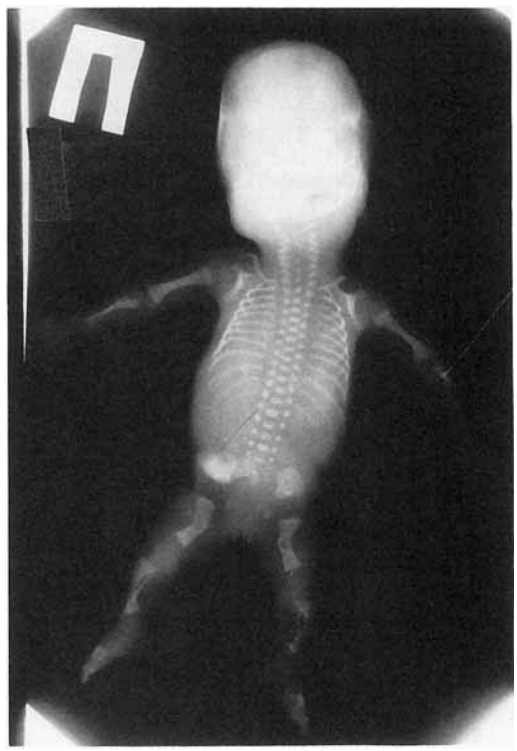

Fig. 11. Radiograph of the sib (case G., 1992) affected with metatropic dysplasia at 17 weeks of gestation.

Fig. 12. Fetus with achondrogenesis type I at 17 weeks of gestation (Case N., 1989). There is almost total absence of ossification of the spine.

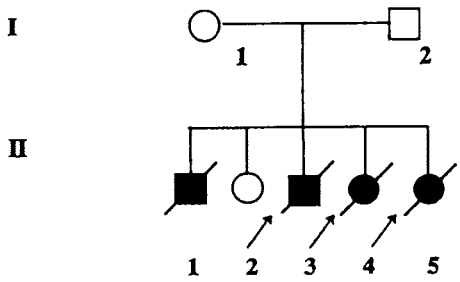

Fig. 13. Pedigree of the family G. with metatropic dysplasia (Mrs. G. = I-1).

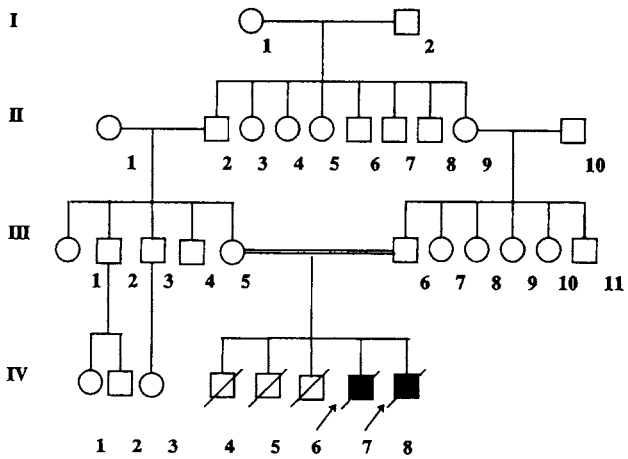

Fig. 14. Pedigree of the family N. with achondrogenesis type I (Mrs. N. = III-5; III-5 and -6 are first cousins).

lage and bone remain essential for precise diagnosis [Qureshi et al., 1995]. A multidisciplinary approach is valuable in elaborating the important implications for genetic counselling also. We conclude that all cases of osteochondrodysplasias need adequate documentation including ultrasonographs, radiographs, photographs, autopsy, and the results of additional chromosomal, biochemical, and DNA analyses. This is necessary for the creation of the data base needed to improve prenatal diagnosis and to help the families with osteochondrodysplasias.

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